Response to Rejections under 35 U.S.C. § 112

Claims 29, 34, 39, 44, 49, and 54 stand rejected under 35 U.S.C. § 112(2) as being indefinite. Specifically, the Examiner asserts that it is unclear as to what "position 8" refers to as no sequence is specified. As stated in the Specification on page 13, native GLP-1 is well known in the art and has the following sequence [SEQ ID NO:1]

^{7}His-Ala-Glu-^{10}Gly-Thr-Phe-Thr-Ser-^{15}Asp-Val-Ser-Ser-Tyr-^{20}Leu-Glu-Gly-Gln-Ala-^{25}Ala-Lys-Glu-Phe-Ile-^{30}Ala-Trp-Leu-Val-Lys-^{35}Gly-Arg-NH_2

It is also well known that the native GLP-1 molecule is processed *in vivo* such that the first 6 amino acids are removed. Only the processed peptide is active. The native molecule is also amidated *in vivo* such that the glycine residue at position 37 is replaced with an amide group. By custom in the art, the amino terminus of GLP-1(7-37)OH has been assigned residue number 7 and the carboxy-terminus, number 37. The other amino acids in the polypeptide are numbered consecutively, as shown in the sequence on page 13 of the Specification. For example, position 12 is phenylalanine and position 22 is glycine. Thus, "a position 8" analog is a peptide with one or more changes relative to native GLP-1 and wherein alanine at position 8 is substituted with another amino acid. One skilled in the art would clearly understand that position 8 refers to the second position in the processed/mature GLP-1 peptide. Thus, Applicants respectfully submit that the metes and bounds of the claim are clear and request the §112(2) rejection be withdrawn.

Rejection under 35 U.S.C. §103

The Examiner has rejected Claims 23 through 55 under 35 U.S.C. § 103 as being unpatentable over Buckley et al., U.S. Patent No. 5,545,618 (hereinafter Buckley) and Ikeda et al., EP 861 666 (hereinafter Ikeda). Claim 56 is also rejected over the same references in view of Jensen et al., WO 96/20005 (hereinafter Jensen). The Examiner asserts that it would have

been *prima facie* obvious to treat diabetes with TZDs and GLP-1 in combination because both GLP-1 and TZDs were known to be useful individually in treating diabetes and Ikeda teaches a method of treating diabetes by combining TZDs with other anti-diabetic compounds that work by a mechanism different from the mechanism by which TZDs work. Further, *In re Kerkhoven*, 205 U.S.P.Q. 1069 (C.C.P.A. 1980) is cited in support of this assertion. Applicants respectfully submit that this rejection should be withdrawn because the Examiner has not established a *prima facie* case of obviousness, the reasoning *In re Kerkhoven* is not applicable to the present application, and even if the Examiner has made a *prima facie* case, the data obtained by Applicants and disclosed in the application is unexpected.

To establish a *prima facie* case of obviousness, it is essential that there be some suggestion to make the claimed invention in light of the prior art cited by the Examiner. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). In the instant case, the references cited by the Examiner do not explicitly or implicitly suggest the claimed combination. The Federal Circuit held that disclosure of a genus covering millions of compounds does not make obvious a claim to three compounds encompassed by the genus without some suggestion to select the claimed compounds. *In re Baird*, 16 F.3d 380 (Fed. Cir. 1994). The court noted that this is especially true when the disclosure indicates preferences leading away from the selected compounds.

This case is similar in that Ikeda discloses combination therapy that encompasses the combination of hundreds of millions of different compounds. Ikeda broadly discloses the use of insulin sensitivity enhancers such as TZDs with anything that has anti-diabetic effects and works through a mechanism other than the enhancement of insulin sensitivity. To support this broad general combination, Ikeda discusses drugs that inhibit certain digestive enzymes, drugs which inhibit the polyol pathway, drugs which stimulate anaerobic glycolysis, drugs which lower blood cholesterol, and drugs such as sulphonylureas which lower blood glucose by enhancing insulin secretion.

Ikeda is written so broadly that no suggestion to make the presently claimed combination exists. Further, there are no preferred combinations exemplified or disclosed that would lead a skilled person to consider pioglitizone and compounds that act through the GLP-1 receptor. Thus, as the court noted in *Baird*, "the fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." 16 F.3d at 382. The prior art generic formula in *Baird* encompassed numerous variables, and the court found the selected compounds patentable over the genus because there was nothing to suggest that one should select the variables that resulted in the selected compounds. *Id.* Similarly, Ikeda presents a broad description (anything that has an anti-diabetic effect and works through a different mechanism) that encompasses millions of different drug combinations to treat diabetes. This does not make the particular combination of piogliztaone and GLP-1 claimed in the present invention obvious.

Considering the Buckley and Jenson references in combination with Ikeda also does not support a suggestion to make the claimed combination with a reasonable expectation of success. This is due to primarily to the unpredictability generally associated with combination therapy. The references cited by the Examiner not only fail to suggest anything with respect to the combination claimed in the present application, but also do not make it possible to predict whether the particular combination claimed herein would be beneficial in the treatment of diabetes. Courts have characterized inventions like the present one as unpredictable because a degree of trial and error is normally required before one can know whether a given strategy will succeed. *See e.g., Ex parte Hitzeman*, 9 U.S.P.Q.2d 1821, 1823 (Bd. Pat. App. & Int. 1988) ("case involves highly unpredictable factors including unique, delicate, and unpredictable biochemical and genetic actions"). This is especially true when one considers combination therapy with compounds that are working through different and often unknown mechanisms and wherein negative drug interactions are a possibility. Treatment of diabetes,

in particular, is associated with numerous side effects and risks. Most notably is the risk of hypoglycemia that results when too much insulin is secreted such that blood glucose levels drop too low.

The Examiner cites *In re Kerkhoven* as supporting the proposition that it is "*prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order for a third composition to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art." The court in that case, however, was focused on claims directed to a process of producing detergent compositions containing a mixture of known active detergent materials. The purpose of the process was to prepare a spray-dried detergent mixture composition wherein it was known that each detergent in the mixture could be spray-dried. Producing a mixture composition is quite different from using two different classes of drugs in combination to treat a particular disease. The present application does not claim a composition with TZDs and GLP-1, but rather claims a method of using these compounds in combination to treat diabetes. The Examiner suggests that when two different things are each known to be useful for the same purpose, it is obvious to combine them and use them for that purpose. This may be true for things like detergent compositions, but cannot extend to a new diabetes therapy.

As mentioned above, just because two different drugs exist that can be used to treat the same disease, does not suggest that the drugs can be or should be used together to treat that same disease. This is further complicated in this case by the fact that GLP-1 has numerous anti-diabetic actions. See Holst, J.J. (2002) Therapy of type 2 diabetes mellitus based on the actions of the glucagons-like peptide-1, *Diabetes Metab Res Rev*, 18:430-441. GLP-1 induces insulin secretion, induces insulin expression, stimulates beta-cell proliferation and differentiation, delays gastric emptying, reduces appetite and food intake, suppresses glucagon, and may even have extra-pancreatic effects. Thus, until the present

invention, it was not known whether GLP-1 which works by these numerous mechanisms would be compatible with TZDs or whether the combination would be at all beneficial in the treatment of diabetes.

If the Examiner is contending the cited references make the invention "obvious to try", this is an improper consideration in adjudicating the obviousness issue. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986). In explaining how "obvious to try" is not the standard, the Federal Circuit held that "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Thus, the general approach described by Ikeda in combination with references describing the known effects of individual compounds (i.e. Buckley and Jensen) cannot make the specific combination encompassed by the present invention obvious.

Finally, even if the Examiner can establish a *prima facie* case, the unexpected effects achieved when administering TZDs with GLP-1 make the invention non-obvious. These effects are disclosed in the application as filed. For example, page 8 of the Specification documents the unexpected effect of enhancing glycemic control while avoiding heart hypertrophy that can occur when TZDs are administered alone. Further, the use of GLP-1 in combination with TZDs avoids risks associated with hypoglycemia that could occur if TZDs are administered with sulphonylureas. Example 1 presents data obtained in diabetic rats which further supports the unexpected beneficial effects that can be obtained when GLP-1 compounds are administered in combination with TZDs.

Thus, because the broad disclosure of Ikeda in view of the known effects of GLP-1 and TZDs does not suggest the claimed combination and because the claimed combination is unexpectedly beneficial, the pending claims are not obvious. Applicants respectfully request the Examiner withdraw this rejection.

Respectfully submitted,

Mark J. Stewart
Attorney for Applicants
Registration No. 43,936
Phone: 317-276-0280

Eli Lilly and Company
Patent Division/MJS
P.O. Box 6288
Indianapolis, Indiana 46206-6288

April 17, 2003